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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,712	10/03/2003	Jillian Cornish	08987-009001 / 9900.99	9880

26161 7590 10/18/2006

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EXAMINER	
BORGEEST, CHRISTINA M	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/678,712	CORNISH ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *19,20 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-18 and 21 are drawn to methods of treating a bone condition comprising administering to a patient FGF-8, an FGF-8 analog or an FGF-8 agonist in the reply filed on 2 August 2006 is acknowledged.

Claims 20 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2 August 2006.

Claim Objections

Claims 1-18 and 21 are objected to because of the following informalities: The claims recite non-elected species (e.g., SEQ ID NOs: 1 and 2). Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims do not recite what an effective amount of FGF-8, FGF-8 analog or FGF-8 agonist is effective to do. For the purpose of

prior art, the claims are interpreted as encompassing administration of FGF-8, FGF-8 analog or FGF-8 agonist to anybody or anything for any purpose. Note that amending the claims to recite what the effective amount of FGF-8, FGF-8 analog or FGF-8 agonist is effective to do would obviate this rejection.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a bone condition characterized by too little bone formation or for increasing or maintaining bone density or for stimulating osteoblast growth comprising administration of SEQ ID NO: 3, does not reasonably provide enablement for administration of FGF-8 variants, fragments or agonists for the treatment of any bone condition or modulating osteoblast apoptosis or for the prevention of osteoporosis, osteopenia, bone defects or osteogenesis imperfecta as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

First, with respect to the claims 1-6, the term "bone condition" is extremely broad and encompasses conditions such as acromegaly or osteosclerotic bone metastasis (in certain cancers), both of which are characterized by too much bone formation. For instance, see Valta et al. (Endorcrinol. 2006; 147: 2171-82), who teach that FGF-8 stimulated osteosarcoma cells (see abstract). The claims encompass therapy and it would not be consistent to administer an agent known to stimulate bone formation in any condition in which too much bone formation occurred.

In addition, with respect to all of the claims, there are issues of breadth, complexity, predictability, direction provided by inventor and existence of working examples concerning the recitation the FGF-8, FGF-8 variants, fragments, analogs or agonists. Evidence as to why the claims as broadly recited are not enabled can be found in Blunt et al. (cited in Applicants 1449 form submitted 30 March 2006). For instance at p. 3735, right column, 1st paragraph, it is stated that:

> None of the FGF-8 isoforms [tested] was able to induce a mitogenic response in BaF3 cells expressing FGFRIb, FGFRIc, FGFR2b, or FGFR3b...BaF3 cell lines expressing FGFR2c and FGFR3c responded to some of the FGF-8 isoforms and to FGF-1 (Fig. 4D and F). FGFR2c-expressing cells responded well to FGF-8f and weakly to FGF-8d, but did not respond to FGF-8e and FGF-8g (Fig. 4D)...

Thus it is clear that all the FGF-8 variants encompassed by the claims would not necessarily be capable of treating any bone condition. Furthermore, in the specification, Applicants discuss the FGF-8 isoforms:

> The significance of these isoforms is unclear. FGF-8b displays the most potent mitogenic activity in vitro as compared to FGF-8a, -8c, -8d, -8e, -8f, and -8g isoforms (Blunt, A. G., et al., supra). FGF-8a does not stimulate mitogenesis through the known FGF receptors, unlike the other FGF-8 isoforms (Blunt, A. G, et al., supra).

According to the working examples in the specification, Applicants found that there was a dose dependent increase in osteoblasts (and decrease in osteoclasts) with administration of the FGF8a isoform, thus while that may provide sufficient evidence that the FGF-8a isoform is enabled, it does not provide any support for all FGF-8 variants, fragments, analogs or agonists. In addition claims reciting agonists in terms of 60% sequence identity, (e.g., claims 5 and 17) it is noted that according to Yao et al. (Brain research. 1999; 818: 140-146), that FGF-13 is 70% homologous to FGF-8, thus the broad claims encompass other FGFs altogether. Finally, the term, "agonist" encompasses small organic molecules, DNA, as well as unrelated proteins.

In general, with regard to FGF-8, FGF-8 variants, fragments, analogs or agonists, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein fragment or variant is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the

protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein that are tolerant to change (e.g. such as "up to 14 conservative amino acid substitutions" or a "fragment of less than 50 amino acids" or simply "fragment", as is recited in the claims), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially

p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Furthermore, because there is no functional on the FGF-8, FGF-8 analog or FGF-8 agonist recited in the claims, the claims encompass administration of non-functional agents for "bone conditions" or "increasing or maintaining bone density" or "stimulating osteoblast growth or modulating osteoblast apoptosis."

Claim 13 recites "modulating" osteoblast apoptosis in the alternative. Modulation implies up- and down-regulation. Example 1 of the specification teaches that FGF-8a stimulated osteoblast proliferation in a dose-dependent manner, thus the claim is not enabled for modulation insomuch as it encompasses up-regulating osteoblast apoptosis.

Finally, claim 21 is drawn to "preventing osteoporosis, osteopenia, bone defects or osteogenesis imperfecta" in the alternative. The plain English meaning of the word prevention implies 100% success at stopping an event from occurring. The claimed methods do not achieve this goal. Therapeutics inhibit symptoms, mechanism and/or the onset of disease, but do not prevent all pathological events from occurring. The use of the word "preventing" in the claims implies that not a single adverse even will occur (i.e. osteoporosis, ostepenia, bone defects or osteogenesis imperfecta, and that is not the case. For instance, Example 1 shows that FGF-8a stimulated osteoblast proliferation in a dose-dependent manner, Example 2, shows that FGF-8a inhibited formation of osteoclasts in bone marrow cultures in a dose-dependent manner and

Example 3 demonstrated that the FGF-8 gene is expressed in fetal rat brain and cultured osteoblasts, and while those are promising data, they do not suggest that all the bone defects recited in claim 21 could be avoided. Furthermore, the entire population is at risk for developing osteoporosis or bone defects, and while the art teaches methods of reducing the risk of these conditions, they cannot be prevented in every case. For instance, a broken bone is always a risk in any vertebrate. The prior art is silent with respect to 100% prevention of every pathological event occurring during the course of a disease or disability after administration of a medicament designed to treat that particular disease or disability.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives (variants, fragments, analogs or agonists) recited in the claims, and screen same for activity as a therapeutic agent for any bone conditions or for modulating osteoblast apoptosis the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention (protein therapy and 100% prevention), the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-18 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Singh et al. (WO 01/00662, published 4 January 2001). The claims recite a method of treating a bone condition or a method for increasing or maintaining bone density or a method for stimulating osteoblast growth or modulating osteoblast apoptosis comprising administering to a patient in need thereof an effective amount of FGF-8, FGF-8 analog, or a FGF-8 agonist, wherein the FGF-8 agonist comprises a fragment or the entirety of the amino acid sequence of SEQ ID NO: 3, and/or wherein the fragment is less than 50 amino acids of SEQ ID NO: 3, and/or wherein the FGF-8 agonist comprises an amino acid sequence that is at least 60% identical to SEQ ID NO: 3, and/or wherein the FGF-8 agonist comprises SEQ ID NO: 3 with up to 14 conservative amino acid substitutions, or a method for treating or preventing osteoporosis, osteopenia, bone defects, or osteogenesis imperfecta, comprising administration to a subject in need thereof an effective amount of FGF-8, FGF-8 analog, or FGF-8 agonist. Note that the claims do

not recite what an effective amount of FGF-8, FGF-8 analog or FGF-8 agonist is effective to do, thusfor the purpose of prior art, the claims encompass administration of FGF-8, FGF-8 analog or FGF-8 agonist to anybody or anything for any purpose.

Singh et al. teach a method of administering an FGF-8 compound with 100% sequence identity (see APPENDIX 1) to SEQ ID NO: 3 of the instant application, or fragments thereof or variants having at least 90% sequence identity for the purpose of treating neurological disorders (see p. 6, entire page, for example). In addition, at p. 8 (last paragraph) to p. 9 (1^{st} – 2^{nd} paragraphs) treatment of spinal cord injuries and trauma is contemplated with the FGF-8 polypeptide. Spinal cord injuries and injuries resulting from trauma almost always involve broken vertebrae and/or other broken bones, thus the treatment of bone disorders is encompassed by the disclosure of the WO 01/00662 document. In addition, because the claims fail to recite what the FGF-8 is effective for (see Rejections under 35 U.S.C. 112, second paragraph), the claims encompass administration of FGF-8, FGF-8 analog or FGF-8 agonist to anybody or anything for any purpose.

Claims 1, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 15, 16, 17, 18 and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Khodadoust et al. (US PGPub: 20030022170, filed 29 March 2001). See the immediately preceding paragraphs for a discussion of what the instant claims encompass.

Khodadoust et al. teach the administration of a composition that has 98.6% similarity with SEQ ID NO: 3 (see APPENDIX 2), or a fragment containing less than 50

amino acids of SEQ ID NO: 3 (see [0012]) for "the purpose of stimulating chondrocyte growth thereby enhancing bone and periodontal regeneration..." (see [0323]). Evidence that the MFGF protein taught by Khodadoust et al. is closely related to FGF-8 can be found at [0358]:

> These cysteine residues occur in the predicted mature protein, but one of these cysteines is not in the position found in all other members of the FGF family, with the exception of FGF-8. While the more carboxy-terminal cysteine of both FGF-8 and MFGF is in the same position as that of the other FGF family members, the more amino-terminal cysteine is uniquely positioned only 18 residues upstream of the more carboxy-terminal cysteine and thus suggests a unique evolutionary relatedness between FGF-8 and MFGF.

Thus the claims do not contribute anything over the prior art, particularly because Khodadoust et al. teach the administration of the polypeptides for the treatment of bone conditions.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Christina Borgeest, Ph.D.

ELIZABETH KEMMERER
PRIMARY EXAMINER

APPENDIX 1

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  Query Match             100.0%;  Score 1070;  DB 4;  Length 204;
  Best Local Similarity   100.0%;  Pred. No. 1.6e-110;
  Matches  204;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MGSPRSALSCLLLHLLVLCLQAQHVREQSLVTDQLSRRLIRTYQLYSRTSGKHVQVLANK 60
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Qy         61 RINAMAEDGDPFAKLIVETDTFGSRVRVRGAETGLYICMNKKGKLIAKSNGKGKDCVFTE 120
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Qy        121 IVLENNYTALQNAKYEGWYMAFTRKGRPRKGSKTRQHQREVHFMKRLPRGHHTTEQSLRF 180
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Db        121 IVLENNYTALQNAKYEGWYMAFTRKGRPRKGSKTRQHQREVHFMKRLPRGHHTTEQSLRF 180

Qy        181 EFLNYPPFTRSLRGSQRTWAPEPR 204
              ||||||||||||||||||||||||
Db        181 EFLNYPPFTRSLRGSQRTWAPEPR 204
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APPENDIX 2

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  Query Match             98.6%;  Score 1054.5;  DB 3;  Length 215;
  Best Local Similarity   94.9%;  Pred. No. 5.7e-104;
  Matches  204;  Conservative    0;  Mismatches    0;  Indels   11;  Gaps    1;

Qy          1 MGSPRSALSCLLLHLLVLCLQA----------QHVREQSLVTDQLSRRLIRTYQLYSRT 49
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Qy        110 NGKGKDCVFTEIVLENNYTALQNAKYEGWYMAFTRKGRPRKGSKTRQHQREVHFMKRLPR 169
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Db        121 NGKGKDCVFTEIVLENNYTALQNAKYEGWYMAFTRKGRPRKGSKTRQHQREVHFMKRLPR 180

Qy        170 GHHTTEQSLRFEFLNYPPFTRSLRGSQRTWAPEPR 204
              |||||||||||||||||||||||||||||||||||
Db        181 GHHTTEQSLRFEFLNYPPFTRSLRGSQRTWAPEPR 215
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